UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/893,666	06/29/2001	Ichiro Yamashita	210217US0	9403

22850 7590 06/30/2003

OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	19

DATE MAILED: 06/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/893,666	Yamashita, I.
Examiner	**Art Unit**
Joseph Woitach	1632

-- ***The MAILING DATE of this communication appears on the cover sheet with the correspondence address*** --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Apr 17, 2003* .

2a) [X] This action is **FINAL.** 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-29* is/are pending in the application.

4a) Of the above, claim(s) *1-5* is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *6-29* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [X] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [X] All b) [ ] Some* c) [ ] None of:

1. [X] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____ .
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s).
4) [ ] Interview Summary (PTO-413) Paper No(s).
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other:

DETAILED ACTION

This application filed June 29, 2001, claims benefit to foreign application No: 2000-247729, filed August 17, 2000 in Japan.

Applicants' amendment filed April 17, 2003, paper number 18, has been received and entered. Claims 6-15 have been amended. claims 18-29 have been added. Claims 1-29 are pending.

Election/Restriction

Applicant's election with traverse of Group III, claims 6-17, in Paper No. 13 was acknowledged in the previous office action. No new arguments have been provided by Applicants, and therefore, the requirement is still deemed proper and is FINAL.

Newly added claims 18-29 are directed to transgenic mekada fish comprising a transgene which expresses the estrogen receptor, methods of making said transgenic fish, and methods of using said transgenic fish, and are encompassed by the elected invention.

Claims 1-29 are pending. Claims 1-5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13. Claims 6-17 as they are drawn to a transgenic mekada fish and use thereof are currently under examination.

This application contains claims drawn to an invention nonelected with traverse in Paper No. 13. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Drawings

A notice of Draftsperson's patent drawing review was provided with the last office action mailed January 17, 2003, paper number 15, which set forth proposed drawing correction and required corrected drawings. Applicants have indicated that no drawings were filed in the instant application. Upon closer inspection of the drawings present in the instant file, it is found that the drawings were intended for PCT/GB97/00875 filed as US Application 09/155,452. Accordingly, the drawings and the draftsperson's review have been removed from the instant application.

Response to Amendment

The declaration of Dr. Kawahara, Dr. Okada and Dr. Yamashita filed on April 21, 2003, paper number 17, under 37 CFR 1.131 is sufficient to overcome the Kawahara *et al.* reference.

Priority

Applicants have not addressed the comments set forth in the previous office action regarding the priority of the instant application. Specifically, receipt was acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the

file. However, Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. Accordingly, it is maintained that the instant application has been given the priority date of its filing, June 29, 2001.

Claim Objections

Claims 6 and 7 objected to for being dependent on non-elected claims is withdrawn. Amendments to the claims has obviated the basis of the objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-17 stand and claims 18-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic medaka fish comprising within its genome a polynucleotide (SEQ ID NO: 1) encoding a medaka estrogen receptor as set forth in SEQ ID NO: 2 operatively linked to the medaka beta-actin promoter, wherein said transgenic medaka fish produces increased level of the estrogen receptor as compared to normal wild type medaka fish and produce observable thrombi when cultured in the presence of estrogen, and methods of use of said transgenic medaka fish in methods to detect estrogen in a sample and to

develop transgenic medaka fish with thrombi, does not reasonably provide enablement for medaka fish which do not express the estrogen receptor, for other promoters besides the beta-actin promoter, or for the use of transgenic medaka fish which do not develop thrombi. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants review the basis of the rejection and note amendments to the claims. In particular, Applicants note that the claims require that of any promoter used, it must result in the production of thrombi in the transgenic fish. See Applicants' amendment pages 5-6. Applicants' arguments have been fully considered, but not found persuasive.

The amendments to the claims are noted, however two primary points remain. The newly added claims are drawn to the same invention and encompass the same limitations and art recognized problems set forth previously for claims 6-17. First, the phenotype of thrombi formation in the transgenic mekada fish is a consequence of estrogen or estrogen-like compounds present in the water, and do not result simply as a consequence of the transgene expression. Second, the resulting phenotype of transgene expression is a direct consequence of the promoter used, involving factors such as levels of expression and cell specific expression of said transgene. Examiner would concede that given the level of skill in the art, the specification provides adequate technical guidance for the construction of a transgenic fish. However, beyond the reduction to practice using the mekada beta actin promoter, the specification provides no other substitute promoters which will function similarly to this mekada promoter or any general or

specific guidance for obtaining an alternate promoter. The specification is silent with respect to the levels of transgene expression required, the requirements of cell specific expression, or any other general concerns the artisan must address in obtaining and successfully using any other promoter besides the mekada beta actin promoter.

As indicated in the previous office action, "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Further, it is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). In the instant case, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims encompass potentially an enormous number of nucleotide promoter sequences, however the specification only teaches a **single** mekada beta actin sequence. Importantly, this sequence is derived from the animal in which is used and it is a promoter with a specific and particular expression pattern. There are no equivalents set forth in the specification or the art of record, and no guidance to the general properties of the promoter which are desired or essential to the functionality in the context of the resulting transgenic mekada fish. As of the effective filing date of the claimed invention, the art of making transgenic animals with a specific and given phenotype was known to be

unpredictable. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). As indicated above, it is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994). In the instant case, there is insufficient guidance and **no** evidence in the specification or the art of record which supports that the enormous number of potential promoters encompassed by the instant claims. Obtaining and empirically trying the enormous number of potential promoters would constitute an enormous amount of experimentation without any clear expectation of success. The reduction to practice with a single promoter sequence is **not** sufficient enablement for Applicant's broadly claimed invention. Accordingly, as the specification provides insufficient guidance and "experiments in genetic engineering produce, at best, unpredictable results" *(Ex parte Forman*, 230 USPQ 546 (BPAI 1986)), it would have required one of skill in the art undue experimentation to test.

35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Further, the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic

> enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material **or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added). This is particularly true in the art of transgenic animals with respect to transgene behavior.

As summarized in the previous office action transgene expression in different species of transgenic non-human animals is not consistent and varies according to the particular host species. Generally, Hammer *et al.* report the production of transgenic mice, sheep and pigs; however only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277). This evidence clearly shows that promoters from various sources will function differently in different species. Further supporting the unpredictability of promoter and transgene behavior Mullins *et al.* state that "a given construct may react very differently from one species to another" (page S39, Summary). More specifically with different species of

fish, Houdebine *et al.* teach that while external fertilization is a natural process and fish embryos can be easily obtained, there are may variations among species development which make the use various species eggs difficult in transgenics (page 891, bottom of second column). With respect to the beta actin promoter, Takage *et al.* (IDS ref AW) teach that the beta actin promoter is a strong promoter capable of providing expression in a wide range of tissues tested (bridging pages 194-195). However, positional silencing was demonstrated in all but one of the transgenic lines developed (page 196, figure 6). In summary, like other transgenic animals, medaka fish demonstrate the same variability in transgene expression as evidenced by the experiments with the beta actin promoter.

With respect to the resulting phenotype, the ability of a estrogen receptor to elicit a specific affect will be a consequence of the specific estrogen receptor expressed, the specific tissues in which it is expressed, the specific levels at which it is expressed and the complexity of the pathway in which it participates. Kawahara *et al.* was cited for the characterization of a related medaka estrogen receptor. Kawahara *et al.* teach that in normal medaka fish, the consequence of estrogen treatment affected expression patterns in different at various stages of fish development. The observable affect seen in normal medaka fish was reversal of the male gonads and may affect bone formation (page 643). Other preliminary results reported by Kawahara *et al.* for a transgenic medaka over-expressing the estrogen receptor is that transgenic fish is affects in particular blood vessel development (page 648). Gray *et al.* (IDS reference) was cited for the teaching that

estrogen treatment of medaka fish can affect a variety of phenotypes beyond sex determination including affecting the central nervous system (page 2587, second column). Clearly in medaka fish the affect of estrogen and the role of the various estrogen receptor variants is a complex system which still remains to be elucidated (Kawahara *et al.* page 648). With respect to the instant claims, clearly the particular expression levels of and tissue specific patterns of expression are important for the resulting phenotype. As noted above, the expression alone of the transgene does not result in thrombi formation, and this point alone is a significant embodiment of the claim which is not enabled by the present specification or the art of record.

The art teaches that the *in vivo* expression of a transgene is dependent on the specific promoters used in the transgene construct, number of copies of the transgene inserted into the host genome, location in the genome and number of cells which contain the transgene can affect the phenotype of the resulting transgenic fish. While the methods for the introduction of a transgene are becoming routine in the art, the expression of the transgene and resulting phenotype of the animal is not predictable. Absent correlative evidence or further guidance in light of the unpredictability of transgene behavior and the complexity of the estrogen receptor *in vivo*, the specification does not reasonably provide enablement for medaka fish which do not express the estrogen receptor, for other promoters besides the beta-actin promoter, or for the use of transgenic medaka fish which do not develop thrombi.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claims 8-13 are unclear in the in the recitation of 'raising the transgenic medaka fish according to claim' because there is no method steps in the claims on which these claims depend, so it is unclear 'according' to what conditions the claims are referring. Claims 6 and 7 encompass a transgenic medaka fish, and amending claims to 8-11 to recite raising the transgenic medaka fish **of** claim' will obviate the basis of the rejection. Dependent claims 14-17 are included in the basis of the rejection because they fail to further clarify the basis of the rejection.

Claims 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claims 10 and 11 are recite and are drawn to 'Medaka fish having one or more thrombi' however the method by which they

are obtained is by culturing transgenic medaka fish described in claims 6 and 7. The claims are confusing because it is not clear if the claim is drawn to any medaka fish having thrombi or transgenic medaka expressing the medaka estrogen receptor. If the claim is drawn only to a normal medaka, lacking any transgene, it is unclear how culturing a transgenic medaka will result in the loss of the transgene. More clearly indicating the type of fish, transgenic or normal, encompassed by the claim would obviate the basis of the rejection.

Claims 12 and 13 unclear in the recitation of 'estrogen-like action' because estrogen-like compounds do not demonstrate an action, rather the have inherent activities. Amending the claims to recite 'estrogen like activity' will obviate the basis of the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 6-1 rejected under 35 U.S.C. 102(e) as being anticipated by Yamashita (EP 1 180 684 A1) is withdrawn.

Applicants note the priority date of the instant application as June 29, 2001 and the claim for priority to JP 2000-2477729. Additionally, it is noted that Ymashita is not a PCT and that it is the counterpart to the present application. Finally, it is noted that Yamashita was published until February 20, 2002. See Applicants amendment page 4. Applicants' arguments have been fully considered.

As indicated above, the instant application has not been benefit of the foreign application filing date because a translation has not been provided. As acknowledged in Applicants arguments, the priority date of the instant application is June 29, 2001. The filing date of EP 1 180 684 A1 is June 27, 2001, however Yamashita (EP 1 180 684 A1) has not designated the United States as a contracting state, therefore EP 1 180 684 A1 does not qualify as a 102(e) type reference. Therefore, the rejection is withdrawn.

Claims 10 and 11 rejected under 35 U.S.C. 102(e) as being anticipated by Kawahara *et al.* (IDS reference AU) is withdrawn.

As noted above, the declaration of Dr. Kawahara, Dr. Okada and Dr. Yamashita filed on April 21, 2003, paper number 17, under 37 CFR 1.131 is sufficient to overcome the Kawahara *et al.* reference.

Conclusion

No claim is allowed. The claims are free of the art of record because the art fails to teach or suggest that expression of SEQ ID NO: 1 as a transgene in a mekada fish would result in thrombi in said transgenic fish in the presence of estrogen. However, the claims are subject to other rejections.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Joseph T. Woitach